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# Long-Term Cardiac Outcome in High-Risk Patients Undergoing Elective Endovascular or Open Infrarenal Abdominal Aortic Aneurysm Repair

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**Abstract** *Objectives:* To assess long-term outcome of patients at high cardiac risk undergoing endovascular or open AAA repair.
*Methods:* Patients undergoing open or endovascular infrarenal AAA repair with ≥3 cardiac risk factors and preoperative cardiac stress testing (DSE) at 2 university hospitals were studied. Main outcome was cardiac event free and overall survival. Multivariate Cox regression analysis was used to evaluate the influence of type of AAA repair on long-term outcome.
*Results:* In 124 patients (55 endovascular, 69 open) the number and type of cardiac risk factors, medication use and DSE results were similar in both groups. In multivariable analysis, adjusting for cardiac risk factors, stress test results, medication use, and propensity score endovascular repair was associated with improved cardiac event free survival (HR 0.54; 95% CI 0.30–0.98) but not with an overall survival benefit (HR 0.73; 95% CI 0.37–1.46). Importantly, statin therapy was associated with both improved overall survival (HR 0.42; 95% CI 0.21–0.83) and cardiac event free survival (HR 0.45; 95% CI 0.23–0.86).
*Conclusions:* The perioperative cardiac benefit of endovascular AAA repair in high cardiac risk patients is sustained during long-term follow-up provided patients are on optimal medical therapy but it is not associated with improved overall long-term survival.


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## Introduction

Patient undergoing abdominal aortic aneurysm repair are at significant risk for both perioperative and long-term cardiovascular events. In particular patients at high cardiac risk might benefit from endovascular AAA repair. However, no randomized trials comparing open and endovascular treatment have been reported on patients at high cardiac risk. For example, less than half of the patients in the DREAM trial (44%) and EVAR-1 trial (43%) had a history of cardiac disease.[1,2] A major limitation of non-randomized comparative studies between open and endovascular surgical procedures conducted so far is the lack of objective criteria for baseline cardiac condition.[3]

Preoperative cardiac stress testing such as dobutamine stress echocardiography (DSE) provides an objective assessment of the presence and extent of coronary artery disease.[4] In a previous study we used this modality to compare perioperative outcome after open or endovascular AAA repair and found that endovascular repair was superior in terms of cardiovascular outcome.[5] The long-term outcome of these high-risk patients however remained ill-defined.

Therefore we expanded the study population of the previous study and conducted long-term follow-up of these patients. The aim of the present study was to evaluate the long-term effect of endovascular AAA repair compared to open AAA repair in patients at clinical high cardiac risk on cardiac complications and mortality.

## Methods

### Patients

The study population was composed of patients with 3 or more cardiac risk factors who underwent elective abdominal aneurysm repair between January 2000 and January 2006 at two tertiary referral centers, Erasmus University Medical Center Rotterdam, the Netherlands and University Medical Center Utrecht, the Netherlands and had a preoperative cardiac stress test. The choice for either repair method was at the discretion of the treating vascular surgeon and was mainly based on anatomical considerations. The study was approved by the Erasmus MC medical ethics committee.

### Preoperative cardiac risk assessment

All patients were routinely screened for cardiac risk factors, including age over 70 years, history of or presence of angina pectoris, previous myocardial infarction, heart failure, stroke, renal failure (serum creatinine $>170\ \mu mol/l$), and diabetes mellitus. The presence of hypertension and chronic obstructive pulmonary disease (COPD) was noted as well. A patient was classified as having COPD at the preoperative screening visit according to symptoms and pulmonary function test (i.e. FEV1 $< 70\%$ of maximal age and gender predictive value). According to the ACC/AHA guidelines all patients with 3 or more cardiac risk factors underwent cardiac stress testing prior to surgery.

Perioperative medication use was noted including ACE-inhibitors, platelet aggregation inhibitors, beta-blockers, calcium antagonists, coumarin derivatives, diuretics, nitrates, and statins. Patients unable to take medication orally perioperatively were switched to intravenous formula. If no intravenous formula was available, i.e. statins and ACE-inhibitors, oral medication was restarted as soon as possible after surgery.

### Cardiac stress testing

Resting echocardiography was used to estimate the left ventricular ejection fraction using the Simpson rule. Cardiac stress testing was performed by dobutamine echocardiography as previously described.[6] Myocardial stress induced ischemia was assessed using a semi-quantitative evaluation; a 5-point score in a 17-segement model. Limited ischemia was defined by the presence of 1–4 ischemic segments, while extensive ischemia was defined by $\geq$5 ischemic segments.

### Outcome

All patients were monitored for cardiac events after abdominal aortic aneurysm repair. Twelve-lead ECG and serum troponin-T levels were systematically determined on days 1, 3, and 7 postoperatively or at discharge. The primary outcome of the study was the incidence of all-cause mortality and the combination of myocardial infarction and all-cause death during long-term follow-up. Myocardial infarction was defined as the presence of 2 out of the following 3 criteria: (1) Characteristic ischemic symptoms lasting $>$ 20 min, (2) electrocardiographic changes including acute ST elevation followed by appearance of Q waves or loss of R waves, or new left bundle branch block, or new persistent T wave inversion for at least 24 h, or new ST segment depression which persists $>$24 h, and (3) a positive troponin T, i.e. $>$0.10 ng/ml, or peak CK-MB $>$8% of an elevated total creatinine phosphokinase with characteristic rise and fall.[7] Survival status was confirmed by contacting the civil service registry.

### Statistical analysis

Continuous data are presented as median values and corresponding 25th and 75th percentiles, whereas dichotomous data are presented as percentages. Differences in clinical characteristics between patients undergoing endovascular repair or open repair were evaluated by Wilcoxon's nonparametric tests, Chi-square tests or Fisher's exact tests, as appropriate. The incidence of events over time was further examined by the Kaplan–Meier method, whereas a log-rank test was applied to evaluate differences between the two treatment modalities. We developed a propensity score for the likelihood of undergoing either open or endovascular AAA repair and used applied multivariate logistic regression analysis to calculate the propensity score. The association of type of AAA repair, cardiovascular risk factors and medication use with long-term events was assessed via multivariate Cox regression analysis, including the propensity score, with stepwise

backward removal. The limit of statistical significance was set at $P = 0.05$ (two sided). All analysis was performed using the statistical software SPSS for Windows 12.0.1 (SPSS Inc., Chicago, Illinois, USA).

## Results

### Patient characteristics

A total of 124 patients with 3 or more clinical cardiac risk factors were included in this study. Of these, 69 patients underwent open AAA repair and 55 patients underwent endovascular AAA repair. Clinical baseline characteristics of these patients are shown in Table 1. Almost all (92%) patients were male, their mean age was $74 \pm 6$ years, and the median AAA diameter was 60 mm (interquartile range 55–70 mm). There were no statistically significant differences between patients undergoing open or endovascular AAA repair in terms of clinical characteristics or medication use. During non-invasive stress testing approximately half (47%) of all patients had stress inducible myocardial ischemia. A total of 46 (37%) patients had mild myocardial ischemia while another 12 (10%) patients had extensive myocardial ischemia. There was no difference in, mild or extensive myocardial ischemia between the open and endovascular group (respectively 54% vs 53%, 35% vs 40% and 12% vs 7%).

### Perioperative outcome

Overall 30-day mortality was 4.3% for the open group and 0% for the endovascular group. An additional 3 (4.3%) patients in the open group died during hospitalization but after 30 days of the index procedure. The combined 30-day endpoint of non-fatal myocardial infarction and all-cause death was 12 (17%) in the open and 2 (4%) in the endovascular group ($p = 0.02$). The length of hospital stay was significantly shorter in patients with endovascular AAA repair (median 3 vs 11 days, $p < 0.001$).

### Long-term outcome

#### Type of repair

During a median follow-up of 3.3 years (interquartile range 1.8–5.6 years) a total of 39 (31%) patients died and a total of 55 (45%) patients reached the combined endpoint of all-cause death and MI. As is shown in Fig. 1a, during long-term follow-up there was no significant difference in overall survival between endovascular and open AAA repair ($p = 0.38$). Also in multivariate analysis patients treated with endovascular had no significant better survival rate (HR 0.73, 95% CI 0.37–1.46, Table 2). However, patients who underwent endovascular AAA repair did have a statistically significant better cardiac event free survival as compared to patients treated with open repair (Fig. 1b, HR 0.54, 95% CI 0.30–0.98, Table 3). It should be noted

**Table 1** Baseline clinical characteristics of patients undergoing open and endovascular abdominal aneurysm repair

| | All patients ($N = 124$) | Open ($N = 69$) | Endovascular ($N = 55$) | $P$ |
|---|---|---|---|---|
| Men | 114 (92%) | 64 (93%) | 50 (91%) | 0.75 |
| Age (mean, SD) | $74 \pm 6$ | $74 \pm 6$ | $74 \pm 7$ | 0.66 |
| Heart rate prior to surgery | $65 \pm 12$ | $66 \pm 13$ | $64 \pm 9$ | 0.23 |
| *Risk factors* | | | | |
| Previous angina pectoris | 77 (62%) | 41 (59%) | 36 (64%) | 0.71 |
| Previous myocardial infarction | 107 (86%) | 60 (87%) | 47 (84%) | 0.80 |
| Previous heart failure | 25 (20%) | 12 (17%) | 13 (23%) | 0.50 |
| Previous CABG or PTCA | 60 (48%) | 33 (48%) | 27 (48%) | 0.99 |
| CVA or TIA | 46 (37%) | 29 (42%) | 17 (30%) | 0.20 |
| Diabetes mellitus | 18 (14%) | 10 (15%) | 8 (14%) | 0.95 |
| Renal failure | 28 (22%) | 14 (20%) | 14 (25%) | 0.67 |
| Systemic hypertension | 52 (42%) | 32 (46%) | 20 (36%) | 0.28 |
| COPD | 48 (38%) | 28 (41%) | 20 (36%) | 0.57 |
| *Stress echocardiography* | | | | |
| No ischemia | 66 (53%) | 37 (54%) | 29 (53%) | 0.66 |
| Limited ischemia | 46 (37%) | 24 (35%) | 22 (40%) | |
| Extensive ischemia | 12 (10%) | 8 (12%) | 4 (7%) | |
| *Medication at screening* | | | | |
| Platelet aggregation inhibitors | 90 (72%) | 40 (73%) | 40 (71%) | 0.84 |
| ACE-inhibitors | 51 (41%) | 32 (47%) | 19 (34%) | 0.15 |
| Diuretics | 42 (34%) | 25 (59%) | 17 (41%) | 0.57 |
| Nitrates | 35 (28%) | 19 (27%) | 16 (29%) | 0.95 |
| Beta-blockers | 108 (86%) | 60 (87%) | 48 (86%) | 0.88 |
| Statins | 78 (63%) | 41 (59%) | 37 (67%) | 0.46 |
| Calcium-antagonists | 42 (34%) | 24 (35%) | 18 (32%) | 0.85 |

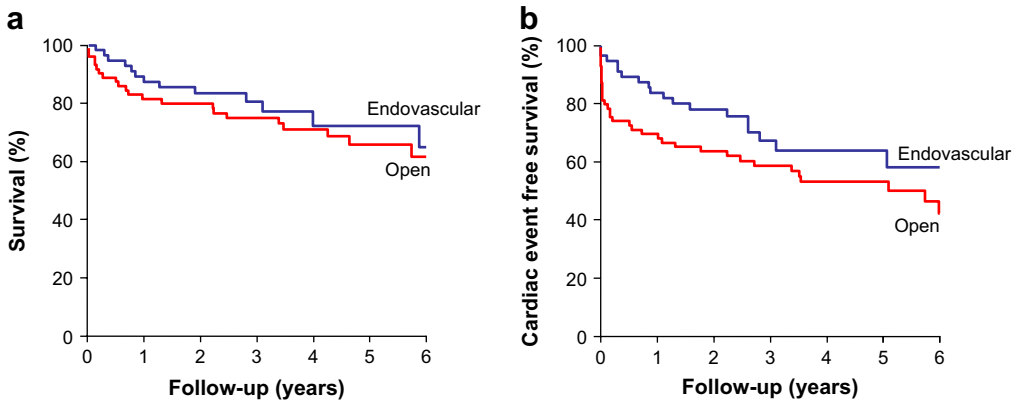


**Figure 1** (a) Overall survival of patients undergoing endovascular or open AAA repair. ■ Open AAA repair. ■ Endovascular AAA repair.(b). Cardiac event free survival of patients undergoing endovascular or open AAA repair. ■ Open AAA repair ■ Endovascular AAA repair.

however that this benefit was mainly driven by the 30-day events. If the first 30 days after surgery are not taken into account there would have been a similar cardiac event free survival among patients treated by endovascular or open repair (HR 0.89, 95% CI 0.44—1.77, $p = 0.73$).

### Medical therapy

While type of AAA repair did not have a significant impact on overall long-term survival aggressive medical therapy did seem to be associated with improved overall survival. Patients on statin therapy had a significant survival benefit over patients not on statin therapy; 5-year overall survival 77% vs 53% respectively (HR 0.42, 95% CI 0.21—0.83, Table 2). Also cardiac survival event free was significantly better in patients on statin therapy (HR 0.45, 95% CI 0.23—0.86, Table 3). As is shown in Fig. 2a, b the perioperative benefit of endovascular repair was only sustained in patients on statin therapy in contrast to patients not on statin therapy (Fig. 3). The prescription rate of statins gradually increased over the studied years, from 38% in 2001/2002 to 67% in 2003/2004 and 88% in 2005/2006 ($p < 0.001$). The vast majority of patients were on beta-blocker therapy. Importantly the mean heart rate prior to surgery was 65 beats per minute, indicating adequate beta-blocker dosing in most patients. However, 35 (28%) patients had inadequate heart rate control with a rate of >70 beats per minute. Patients on adequate beta-blocker therapy had a significantly better overall survival (HR 0.26, 95% CI 0.13—0.54, Table 2) and cardiac event free survival (HR 0.53, 95% CI 0.29-0.97, Table 3). Importantly, there was no significant interaction between statin use and adequate beta-blocker dosing. Furthermore, as shown in Table 2 patients who were on platelet aggregation inhibitors had a better overall survival than did patients who were not on antiplatelet therapy (HR 0.47; 95% CI 0.23—0.97, $p = 0.04$).

## Discussion

This study showed that, despite a reduced incidence of adverse perioperative events, endovascular repair of elective infrarenal AAA in cardiac high-risk patients has a similar long-term survival, compared to patients undergoing open AAA repair. However, the perioperative cardiac benefit is sustained during a median follow-up of 3.3 years in this high-risk population provided patients are on optimal medical therapy. Furthermore, aggressive medical treatment seems to have more impact on overall and cardiac event free survival than does the choice of AAA treatment modality.

Patients undergoing major noncardiac surgery are at significant risk of cardiovascular morbidity and mortality. The prognosis after vascular surgery is predominantly

**Table 2** Significant predictors of long-term overall survival status when clinical characteristics, propensity score for type of surgery, medication use and year of surgery were entered as independent variables into a Cox regression model with stepwise backward removal

| | HR | 95% CI | *P*-value |
|---|---|---|---|
| Endovascular treatment | 0.73 | 0.37—1.46 | 0.37 |
| Age (per year increase) | 1.10 | 1.03—1.17 | 0.003 |
| Stress inducible myocardial ischemia | 1.95 | 1.03—3.89 | 0.04 |
| Statin use | 0.42 | 0.21—0.83 | 0.01 |
| Heart rate <70 bpm | 0.26 | 0.13—0.54 | <0.001 |
| Platelet aggregation inhibitor | 0.47 | 0.23—0.97 | 0.04 |

**Table 3** Significant predictors of long-term cardiac event free survival status when clinical characteristics, propensity score for type of surgery, medication use and year of surgery were entered as independent variables into a Cox regression model with stepwise backward removal

| | HR | 95% CI | *P*-value |
|---|---|---|---|
| Endovascular treatment | 0.54 | 0.30—0.98 | 0.04 |
| Age (per year increase) | 1.05 | 1.01—1.10 | 0.03 |
| Stress inducible myocardial ischemia | 2.60 | 1.45—4.67 | 0.001 |
| Statin use | 0.45 | 0.23—0.86 | 0.02 |
| Heart rate <70 bpm | 0.53 | 0.29—0.97 | 0.04 |

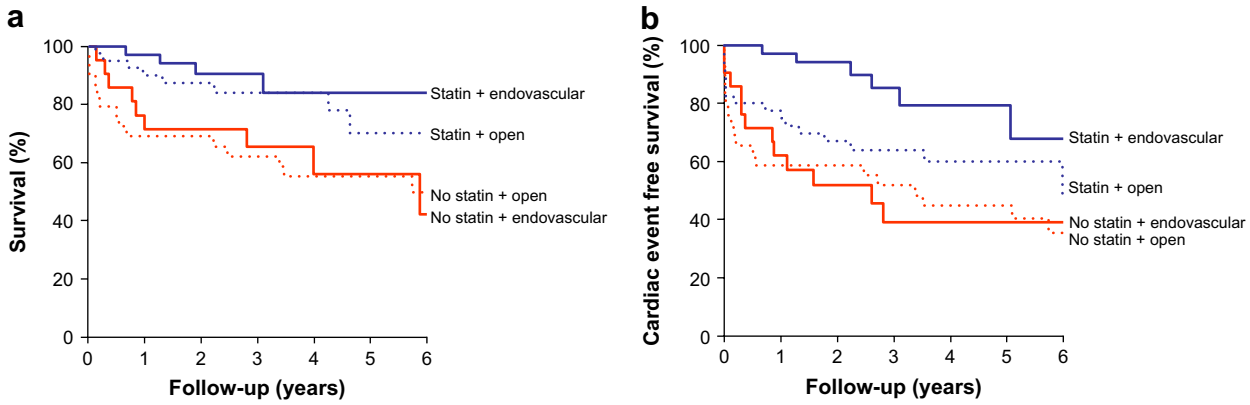


**Figure 2** (a) Overall survival of patients undergoing endovascular or open AAA repair, divided into statin users or non-users. ■ ■ Statin users undergoing open AAA repair ■ Statin users undergoing endovascular AAA repair ■ ■ Non-users undergoing open AAA repair ■ Non-users undergoing endovascular AAA repair. (b). Cardiac event free survival of patients undergoing endovascular or open AAA repair, divided into statin users or non-users. ■ ■ Statin users undergoing open AAA repair. ■ Statin users undergoing endovascular AAA repair. ■ ■ Non-users undergoing open AAA repair ■ Non-users undergoing endovascular AAA repair.

determined by the presence and extent of underlying coronary artery disease.[8] In the landmark study performed over 20 years ago Hertzer et al. found that only 8% of a group of 1000 patients undergoing noncardiac vascular surgery had normal coronary angiography results.[9] This high prevalence of underlying cardiac disease has later also been confirmed by functional tests such as dobutamine stress echocardiography.[10] Considering this high prevalence of coronary artery disease in vascular surgery patients it is hardly surprising that cardiac death after AAA repair accounts for approximately 40% and 65% of all 30-day and long-term mortality, respectively.[11] It might be argued that optimal medical therapy is warranted to sustain the initial cardiovascular survival benefit in patients who underwent endovascular AAA repair.

In previous studies perioperative and long-term statin therapy have been associated with improved outcome in patients undergoing AAA repair. Several recent retrospective studies have shown a beneficial effect of statins on perioperative cardiac outcome with adjusted hazard ratio's ranging from 0.20 to 0.62.[12] Importantly, Kertai et al. also found the effect of statins to be independent of β-blocker use.[13] So far only one placebo-controlled, randomized trial has investigated the influence of statin use on perioperative cardiovascular complications. In a group of 100 patients treatment with 20 mg of atorvastatin was associated with a significant 3.1-fold ($p = 0.022$) reduction in cardiovascular complications within 6 months after vascular surgery.[14] Kertai et al. described the influence of statin use on long-term outcome after open AAA repair in 570 patients with a median follow-up of 4.7 years.[15] It was shown that, in this group of unselected AAA patients, statin use was associated with a 2.5-fold reduction in the risk of all-cause mortality (HR 0.4; 95% CI 0.3—0.5) and a 3-fold reduction in the risk of cardiovascular mortality (HR 0.3; 95% CI 0.2—0.6). Interestingly, the present study included only high cardiac risk patients but the reduction in the risk for mortality and cardiovascular complications was similar to the reported figures of Kertai et al.

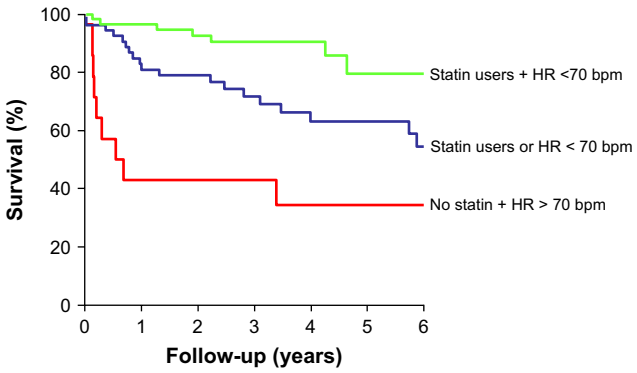


**Figure 3** Overall survival of patients undergoing endovascular or open AAA repair, divided into patients not on adequate beta-blocker therapy and statin therapy, patients on either adequate beta-blocker therapy or statin therapy, and patients on both adequate beta-blocker therapy and statin therapy. ■ Statin therapy and adequate beta-blocker therapy. ■ Statin therapy or adequate beta-blocker therapy ■ No statin therapy and no adequate beta-blocker therapy.

Importantly statin use is advocated in the recent TASC II document.[16] Patients with symptomatic or asymptomatic peripheral arterial disease should have their LDL lowered to less than 2.59 mmol/l. Patients with multiple vascular beds affected should be treated even more aggressively with a target LDL <1.81 mmol/l. It should be noted that the cardioprotective effect of statins might not only be by reducing LDL levels but statins might also exert their protective effects by so-called pleiotropic effects.

Another medical intervention that has been proven successful in high-risk patients undergoing major vascular surgery is beta-blocker therapy. In the DECREASE I trial patients with preoperative stress inducible myocardial ischemia had a mere 10-fold reduction in perioperative cardiac events compared to patients who received placebo treatment.[17] Additionally, during a median follow-up of 22 months only 12% of patients on beta-blocker therapy experienced a cardiac event vs 32% of the patients who

were not on beta-blocker therapy ($p = 0.025$).[18] This treatment effect was later confirmed in the DECREASE I registry patients in which 1299 survivors of vascular surgery were followed for a median duration of 23 months.[19] In multivariable analysis the 360 patients on beta-blockers had a significant risk reduction for cardiac events (HR 0.3; 95% CI 0.2–0.6; $P < 0.001$). However, recently some trials were published that questioned the potential benefit of beta-blockers in vascular surgery patients. In particular the POISE trial might have a negative impact on the willingness to prescribe beta-blockers to patients undergoing major vascular surgery. In the POISE trial the investigators found an increased risk for all-cause death in patients using beta-blockers, in particular driven by an excess in perioperative strokes.[20] There are several explanations for the findings in POISE related to dosing, duration of therapy, beta-blocker withdrawal and adequate titration.[21] When keeping this in mind, beta-blocker therapy still is safe and effective, in particular in patients at high cardiac risk as in the current study.

It should be noted that the patients in the current study were considered to be at high cardiac risk which does not imply that they were considered to be unfit for surgery in general. The term cardiac high-risk in this study is based on our observations in the DECREASE I and II trials.[22] Patients with 3 or more risk factors as in the present study had a 4-fold and 28-fold increased risk for perioperative cardiac events as compared to patients at intermediate or low risk respectively. In terms of overall survival, patients in the current study had a worse outcome compared to patients in EVAR-1 and DREAM but a much better outcome compared to patients in EVAR-2.[1,23,24] Furthermore, the current study is not a randomized trial and as such has obvious limitations related to the nature of the study. However, keeping these limitations in mind, and using multivariable regression analysis with propensity scoring, the results of this study are in line with previous published studies. It reemphasizes the need for optimal medical therapy in high-risk patients scheduled for AAA repair irrespective of the choice of treatment modality. Physicians should not be pacified by the thought that endovascular treatment is a less invasive treatment, therefore being less stressful for the heart and hence requiring less aggressive medical therapy. On the contrary, in the end patients undergoing endovascular AAA repair could even benefit more from aggressive medical therapy as the initial benefit of endovascular repair might be sustained in these patients.

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